IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : Masaya TANAKA
Serial No. 10/520,100
Filed: January 4, 2005
For: CARBON DIOXIDE EXTERNAL PREPARATION, AND MATEERIAL FOR FORMATION OF CARBON DIOXIDE EXTERNAL PREPARATION

Art Unit: 1619
Examiner: Kassa, TIGABU

DECLARATION

Honorable Commissioner for Patents
Sir

I, Masaya TANAKA, a citizen of Japan, declare as follows:

I graduated from Graduate School of Engineering Osaka University, majored in chemistry and obtained BSc and MSc degrees from the above university March, 1978 and March, 1980 respectively.

From 1980, I was employed in Kanebo Co. Ltd., and engaged in research and development on external drugs.

After leaving the said company in 1997, I made my own research in transdermal drug delivery technique in Kobe Pharmaceuticals University for three years.

I am an inventor of this US Application No.10/520,100 filed on January 4, 2005, and familiar with the subject matter thereof.

Comparative Experiment on Effectiveness of Carbon Dioxide External Preparations

1. Purpose of the Experiment

This experiment was conducted in order to compare the efficacy of the carbon dioxide external preparations of the present invention with of the cited patent EP1043023.

Vasodilation was chosen as the key action of carbon dioxide external preparations because it is deeply connected with carbon dioxide's unique effects such as wound healing acceleration and anti-aging of the skin.

The following experiment was entirely directed and supervised by the inventor of the present invention, Masaya Tanaka.

Materials and methods

2. Preparation of carbon dioxide external preparations

Practical examples 6 and 13 of the present invention, using a 0.4 mm-thick polyester nonwoven cloth as a polymeric three-dimensional network structure (referred to as Practical Examples), and the compositions 112 and 125 of the cited patent (referred to as Comparative Examples), were chosen as representative preparations or compositions of each patent because their formulations are thought similar. Comparative Examples were used in the experiment as the external preparations (referred to as Modified Comparative Examples) that were impregnated into a 0.4 mm-thick gauze or sponge.

Practical Example 6

(Preparation of base agent)

A viscous material was prepared by mixing 1 part by weight of tartaric acid as an acid, 3 parts by weight of polyvinyl pyrrolidone as a thickener, 0.1 parts by weight of methylparaben as a preservative, and 95.9 parts by weight of purified water as water. Using a 0.4 mm-thick polyester nonwoven cloth as a polymeric three-dimensional network structure, 0.018g of the aforementioned viscous material per square centimeter of the nonwoven cloth was impregnated therein, thus preparing a base agent.

(Preparation of reactant)

A viscous material was prepared by mixing 2 parts by weight of sodium hydrogen carbonate as a carbonate, 6 parts by weight of sodium alginate as a thickener, 0.1 parts by weight of methylparaben as a preservative, and 91.9 parts by weight of purified water at 60°C as water, and then the viscous material was cooled to 2°C, thus preparing a hydrogel-like reactant.

The base agent and the reactant obtained were combined to constitute a material for formation of carbon dioxide external preparation.

Practical Example 13

(Preparation of base agent)

A viscous material was prepared by mixing 1 part by weight of carboxyvinyl polymer as an acid and also a thickener, 2 parts by weight of sodium alginate as a thickener, 0.1 parts by weight of methylparaben as a preservative, and 96.9 parts by weight of purified water as water. Using a 0.4 mm-thick polyester nonwoven cloth as a polymeric three-dimensional network structure, 0.09 g of the above viscous material per square centimeter of the nonwoven cloth was impregnated therein, thus preparing a base agent.

(Preparation of reactant support)

A viscous liquid reactant was prepared by mixing 1 part by weight of sodium hydrogen carbonate as a carbonate, 1 part by weight of sodium alginate as a thickener,

and 98 parts by weight of purified water as water. Using a 0.4 mm-thick polyester nonwoven cloth having a polyethylene film laminated thereon as a closing covering material, 0.09 g of the above reactant per square centimeter of the nonwoven cloth was supported thereon, thus preparing a reactant support.

The base agent and the reactant support obtained were combined to constitute a material for formation of carbon dioxide external preparation.

Modified Comparative Example 112
(Granular acid)

29 parts by weight of croscarmellose sodium, 41 parts by weight of erythritol, and 6 parts by weight of D-sorbitol, as the matrix bases were dispersed in water as solvent, then 24 parts by weight of citric acid as acid was dissolved therein with fully stirring, and the resulting dispersion was heated in an oven to remove the solvent and dry the residue. After the residue solidified, the solid was pulverized into granules.
(Carbonate-containing aqueous viscous composition)

2.4 parts by weight of sodium hydrogen carbonate as carbonate, was dissolved in 89.6 parts by weight of purified water. Then, the above solution was gradually added to 3.0 parts by weight of sodium alginate, 4.0 parts by weight of carboxymethyl starch sodium, and 1.0 part by weight of xanthan gum as thickeners, and stirred at room temperature. After all materials were mixed, the mixture was left to stand overnight to obtain a uniformly dispersed viscous composition.

A composition for preparing a carbon dioxide-containing viscous composition was obtained by combining the above granular acid and the above carbonate-containing aqueous viscous composition. The mixing ratio of the carbonate-containing aqueous viscous composition to the granular acid was set at 20.8:1 by weight.

A carbon dioxide external preparation was obtained by mixing the said carbonate-containing aqueous viscous composition and the said granular acid at the said mixing ratio, and 0.4 mm-thick gauze was impregnated with the resulting mixture.

Modified Comparative Example 125
(Granular acid)

46 parts by weight of xylitol as the matrix base was heated to be melted in water bath, then 39 parts by weight of croscarmellose sodium as the matrix base, and 15 parts by weight of citric acid as acid was dispersed therein with fully stirring. The mixture was left at room temperature until it solidified. Then the solid was pulverized into granules.
(Carbonate-containing aqueous viscous composition)

2.4 parts by weight of sodium hydrogen carbonate as carbonate, was dissolved in 90.6 parts by weight of purified water. Then, the above solution was gradually added to 2.0 parts by weight of sodium alginate, 3.0 parts by weight of carboxymethyl starch sodium, and 2.0 parts by weight of xanthan gum as thickeners, and stirred at room temperature. After all materials were mixed, the mixture was left to stand overnight to obtain a uniformly dispersed viscous composition.

A composition for preparing a carbon dioxide-containing viscous composition was obtained by combining the above granular acid and the above carbonate-containing aqueous viscous composition. The mixing ratio of the carbonate-containing aqueous viscous composition to the granular acid was set at 20.8:1 by weight.

A carbon dioxide external preparation was obtained by mixing the said carbonate-containing aqueous viscous composition and the said granular acid at the said mixing ratio, and 0.4 mm-thick gauze was impregnated with the resulting mixture.

3. Test method

External Preparations tested;

Practical Example 6

A 0.4 mm-thick polyester nonwoven cloth (4 cm×4 cm square piece) impregnated with 1.44g of the base agent of Practical Example 6 was applied to the forearm of the subject. Then 0.72g of the reactant was spread over the above cloth for the generation of carbon dioxide.

Practical Example 13

A 0.4 mm-thick polyester nonwoven cloth (4 cm×4 cm square piece) impregnated with 1.44g of the base agent of Practical Example 13 was applied to the forearm of the subject. Then a reactant support, which is 0.4 mm-thick polyester nonwoven cloth (0.4mm thick, 4 cm×4 cm square piece) impregnated with 1.44g of the reactant of Practical Example 13, was placed over the above cloth for the generation of carbon dioxide.

Modified Comparative Example 112

A carbon dioxide-containing viscous composition was obtained by mixing 0.0288g of the granular acid and 0.6g of the carbonate-containing aqueous viscous gel of Modified Comparative Example 112. The said composition was pressed into a gauze (0.4 mm thick, 4 cm×4 cm square piece).

Modified Comparative Example 125

A carbon dioxide-containing viscous composition was obtained by mixing 0.0288g of the granular acid and 0.6g of the carbonate-containing aqueous viscous gel of Modified Comparative Example 125. The said composition was pressed into a sponge (0.4 mm thick, 4 cm×4 cm square piece).

Subjects; 4 females

Test Procedure

1) The four carbon dioxide external preparations (Practical examples 6 and 13; Modified Comparative examples 112 and 125) were marked A – D randomly and allotted to each subject.

2) Each subject immediately applied the prepared carbon dioxide external preparations on her forearm and evaluated bubble formation and vasodilation according to the evaluation methods, criteria and scores below.

3) The key controller summed up the scores for Evaluation Items for each example.

4. Results

As shown in Table 1 below, bubbles were not observed with naked eyes in the carbon dioxide external preparations of the Practical Example 6 and 13 when they were applied to the forearm . Table 2 shows that carbon dioxide external preparation obtained from the Practical Example 6 of the present invention showed an excellent vasodilatation (For all of the subjects, the Practical Example 6 applied skin turned evenly strongly red within a minute.). After a minute, in 3 of 4 subjects an obvious vasodilatation at the Practical Example 13 applied skin was observed. The vasodilatation still continued after five minutes of the application.

On the other hand, many bubbles were observed in the carbon dioxide external preparation of the Modified Comparative Example 112. Vasodilation was hardly observed or only around the granular acid in spots after 1 minute of application to the skin. Vasodilation was still weaker or only around the granular acid in spots after 5 minutes of application. When the carbon dioxide external preparation of the Modified Comparative Example 125 was applied to the forearm, in 2 of 4 subjects faint or limited (only around the granular acid in spots) vasodilation was observed during the application.

This result indicates that the carbon dioxide-generating reaction between an acid and a carbonate generally proceeds rapidly in the presence of water, and hence most of the carbon dioxide generated in a preparation forms bubbles and is discharged into the atmosphere, and hence the generated carbon dioxide is not used in transdermal absorption, and thus cosmetic or medical effects are hard to obtain.

5. Conclusion

The results shown in Table 1 and 2 clearly indicate that the carbon dioxide external preparations of the present invention are superior to the external preparations using sponge or gauze impregnated with a composition for preparing a carbon dioxide-containing viscous composition of the cited patent.

Table 1

Composition / Evaluation Item	Practical Example 6	Practical Example 13	Modified Comparative Example 112	Modified Comparative Example 125	Subject
1. Bubble formation just after application	0	0	1	0	No.1
	0	0	1	1	No.2
	0	0	1	0	No.3
	0	0	0	0	No.4
Total	0	0	3	1	
2. Bubble formation after 1min of application	0	0	1	1	No.1
	0	0	1	1	No.2
	0	0	1	1	No.3
	0	0	0	0	No.4
Total	0	0	3	3	
3. Bubble formation after 2 min of application	0	0	1	0	No.1
	0	0	0	0	No.2
	0	0	1	1	No.3
	0	0	0	0	No.4
Total	0	0	2	1	
4. Bubble formation after 3 min of application	0	0	1	0	No.1
	0	0	0	0	No.2
	0	0	1	0	No.3
	0	0	0	0	No.4
Total	0	0	2	0	
5. Bubble formation after 5min of application	0	0	1	0	No.1
	0	0	0	0	No.2
	0	0	1	0	No.3
	0	0	0	0	No.4
Total	0	0	2	0	
Gross	0	0	12	5	

Table 2

Composition / Evaluation Item	Practical Example 6	Practical Example 13	Modified Comparative Example 112	Modified Comparative Example 125	Subject
1. Vasodilation (skin redness) after 1min of application	2	1	1	1	No.1
	0	1	0	0	No.2
	2	1	1	0	No.3
	2	0	1	0	No.4
Total	6	3	3	1	
2. Vasodilation (skin redness) after 2min of application	2	2	1	1	No.1
	1	1	0	0	No.2
	2	2	1	0	No.3
	2	1	0	0	No.4
Total	7	6	2	1	
3. Vasodilation (skin redness) after 3min of application	2	2	1	1	No.1
	1	2	0	0	No.2
	2	2	1	1	No.3
	1	1	0	0	No.4
Total	6	7	2	2	
4. Vasodilation (skin redness) after 5min of application	0	2	0	0	No.1
	0	2	0	0	No.2
	1	2	1	1	No.3
	0	1	1	0	No.4
Total	1	7	2	1	
Gross	20	23	9	5	

Evaluation methods, evaluation criteria and scores;

1. Bubble formation just after application or after 1, 2, 3, 5 min of application

Each subject evaluated the bubble formation just after application of the preparations or after 1, 2, 3, 5 min of application with the following scores according to the bubble quantity below.

2 : more than 30% area of the test material contains bubbles
1 : less than 30% area of the test material contains bubbles
0 : no bubbles observed

2. Vasodilatation (skin redness) after 1, 2, 3, 5 min of application

Each subject evaluated the degree of vasodilatation (redness of the skin) after 1, 2, 3, 5 min of the application of the preparations with the following scores according to the criteria below.

2 : strong/distinctive/whole-area skin redness was observed
1 : mild/obscure/spotted skin redness was observed
0 : no skin redness was observed

All statements made herein of our own knowledge are true and all statements made an information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

This 8 day of July, 2009

Tanaka. M

Masaya TANAKA